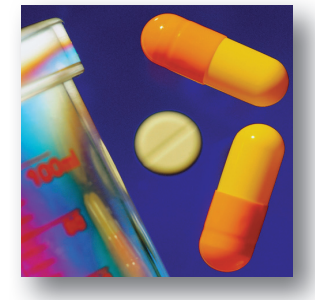

Probuphine (Buprenorphine) Subdermal Implants for the Treatment Of Opioid-Dependent Patients

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INTRODUCTION

New treatments are needed to stem the rise of drug-overdose and opioid-involved deaths in the United States. Prescription opioid pain relievers (such as extended-release oxycodone and hydrocodone/acetaminophen); antianxiety sedatives (such as diazepam and alprazolam [Xanax, Pharmacia & Upjohn Company LLC]); and stimulants for attention-deficit/hyperactivity disorder (ADHD) (such as those containing amphetamine or methylphenidate) are commonly misused to self-treat for medical problems or are abused for purposes of getting high or (especially with stimulants) improving performance.[1] According to the Centers for Disease Control and Prevention (CDC), deaths from prescription opioids have more than quadrupled since 1999. Currently, the CDC estimates that 91 Americans die from an opioid overdose every day.[2]

Effective medications are available for the treatment of opioid-dependent patients. They include buprenorphine, methadone, and extended-release naltrexone (Vivitrol, Alkermes).[3] The World Health Organization has designated buprenorphine and methadone as "essential medications."[4] According to the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, pharmaceutical therapies should be combined with behavioral counseling for a "whole-patient" approach, known as medication-assisted treatment (MAT), in opioid-addicted patients.[3]

Probuphine (buprenorphine implant for subdermal administration CIII, Titan Pharmaceuticals/Braeburn Pharmaceuticals) was cleared by the Food and Drug Administration in May 2016 for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product. It is the only buprenorphine implant approved for this indication[5,6] and is the only product on the market for opioid addiction that provides nonfluctuating blood levels of buprenorphine continuously for six months after a single implant procedure.[7] Probuphine, which uses a proprietary drug-delivery platform called ProNeura, is supplied in a set of four small implants that each contain 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride) and are inserted through a small subdermal incision. It is marketed in the U.S. by Braeburn Pharmaceuticals under a licensing agreement with Titan.[7]

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CLINICAL PHARMACOLOGY[6]

Mechanism of Action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

Pharmacodynamics

Four buprenorphine subdermal implants deliver blood levels of circulating drug that are comparable with average plasma concentrations after daily doses of 8 mg or less of Subutex (buprenorphine, Indivior) or Suboxone (buprenorphine/naloxone, Indivior) tablets or generic equivalent.

Pharmacokinetics

Absorption

In pharmacokinetic trials, the median time to maximum plasma concentration of buprenorphine was 12 hours after Probuphine insertion. After the initial buprenorphine peak, plasma buprenorphine concentrations decreased slowly, and steady-state plasma levels were reached by approximately week 4. Mean steady-state plasma buprenorphine concentrations were approximately 0.5 ng/mL to 1.0 ng/mL and were maintained for approximately 20 weeks during a 24-week treatment period.

Distribution

Buprenorphine is approximately 96% protein bound.

Metabolism

Buprenorphine undergoes both N-dealkylation to its major metabolite, norbuprenorphine, as well as glucuronidation. The N-dealkylation pathway is mediated primarily by cytochrome P450 (CYP) 3A4 enzymes in the liver.

Elimination

Buprenorphine is excreted mainly in the feces (69%) and to a lesser extent in the urine (30%). Based on studies of buprenorphine/naloxone, buprenorphine has a mean elimination half-life ranging from 24 hours to 48 hours.

PIVOTAL CLINICAL STUDY[6]

The efficacy of Probuphine subdermal implants was demonstrated in a randomized, double-blind, double-dummy study in 177 adults who had opioid dependence as their primary diagnosis and who were clinically stable on a sublingual buprenorphine dosage of no more than 8 mg per day as a Suboxone tablet. Most of the patients identified prescription opioid pain relievers as their primary opioid of abuse.

The patients were randomly assigned to receive four buprenorphine implants and placebo sublingual tablets (n = 87) or sublingual buprenorphine/naloxone tablets and placebo implants (n = 89). The patients were evaluated monthly for six months and were required to provide four randomly scheduled urine samples for toxicology. The efficacy of the buprenorphine implants was evaluated via urine toxicology screening and patient self-reports during the six-month treatment period. Supplemental dosing with open-label sublingual buprenorphine/naloxone tablets was permitted, as clinically indicated.

In the group treated with buprenorphine implants, 63% (55 of 87) showed no evidence of illicit opioid use throughout the six-month study period compared with 64% (57 of 89) of the patients given sublingual buprenorphine. Eleven patients (13%) receiving buprenorphine implants required supplemental sublingual buprenorphine but had no evidence of opioid use.

SAFETY CONSIDERATIONS[6]

Boxed Warning

The labeling for Probuphine includes a boxed warning regarding the potential for implant migration, protrusion, expulsion, and nerve damage associated with insertion and removal.

Because of the risks associated with Probuphine implants, the treatment is available only through a risk evaluation and mitigation strategy program, which requires all health care providers to successfully complete a live training program on the insertion and removal procedures and become certified before performing insertions or prescribing it. Patients must be monitored to ensure that Probuphine is removed by a health care provider certified to perform insertions.

Drug Abuse and Dependence

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act. As with morphine and other opioids, buprenorphine can be abused and is subject to criminal diversion. Chronic administration of buprenorphine produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper.

Adverse Events

The safety of buprenorphine was evaluated in a total of 349 opioid-dependent patients in three double-blind trials (n = 309) and two open-label extension studies (n = 40). In these studies, 258 patients were exposed to buprenorphine for at least 24 weeks, and 82 patients were exposed for 48 weeks.

Patients in the buprenorphine arms were treated with four or five implants and may have received supplemental sublingual buprenorphine. Patients in the comparator arms (n = 317) received placebo and either regularly dosed or as-needed sublingual buprenorphine; some patients had placebo implants.

The most common adverse events associated with buprenorphine included headache (13%), nausea, vomiting, and constipation (6% each).

Drug–Drug Interactions

Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4 enzymes; therefore, potential interactions may occur when buprenorphine is administered with agents that affect CYP3A4 activity.

Post-marketing reports of coma and death have been associated with the concomitant use of buprenorphine and benzodiazepines. In many of these cases, buprenorphine was misused by self-injection.

Serotonin syndrome has resulted from the concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system.

Contraindications

Probuphine implants are contraindicated in patients with a history of hypersensitivity to buprenorphine or to any other ingredients in Probuphine.

Use in Specific Populations

Adequate and well-controlled studies have not been conducted with Probuphine or buprenorphine in pregnant women. Nursing mothers receiving buprenorphine should monitor their infants for increased drowsiness and breathing difficulties.

The safety and efficacy of Probuphine implants have not been established in patients younger than 16 years of age. Moreover, clinical studies of Probuphine did not include patients older than 65 years of age.

The effect of hepatic impairment on the pharmacokinetics of implanted buprenorphine has not been studied, and clinical trials of Probuphine did not include patients with renal impairment.

DOSAGE AND ADMINISTRATION[6]

Each Probuphine implant is a soft, flexible, rod-shaped ethylene vinyl acetate implant that is 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride).

Probuphine implants should be used only in opioid-tolerant patients. Each dose consists of four implants inserted subdermally in the inner side of the upper arm. The implants are intended to stay in place for six months of treatment and are then removed.

P&T COMMITTEE CONSIDERATIONS

The NIDA has called Probuphine a "game-changer in fighting opioid dependence."[7] It is the only buprenorphine product available in the form of subcutaneous implants. Competing buprenorphine medications include an intravenous (IV)/intramuscular (IM) injection (Buprenex, Indivior), a buccal film (Belbuca, BioDelivery Sciences International), and a transdermal patch (Butrans, Purdue Pharma) (Table 1).[8–10] Probuphine implants provide patients with continuous buprenorphine for six months before removal, which is an extended period of time compared with the need for more-frequent administration of IM or IV injections, sublingual tablets, sublingual and buccal films, and transdermal patches.[6,8–15]

Other potential benefits include:[7]

- A lower risk of diversion compared with current daily-dosed formulations
- Nonfluctuating blood levels of buprenorphine compared with the variable levels of medication associated with sublingual dosing
- Greater adherence compared with oral and transdermal formulations
- Convenience for frequent travelers (no need for daily administration)
- Fewer office visits

In addition, buprenorphine sublingual products have been implicated in

Table 1 Select Buprenorphine Products Currently on the Market[6,8–17]

Drug *Manufacturer*	Description	Indication(s)	Dosing Regimen	AWP (Six Months)[a]
Belbuca *BioDelivery Sciences International*	Buprenorphine buccal film	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	75-mcg film applied once daily or, if tolerated, every 12 hours for at least four days in opioid-naïve and opioid-nontolerant patients; increase dose to 150 mcg every 12 hours.	$2,006
Bunavail *BioDelivery Sciences International*	Buprenorphine/naloxone buccal film	• Induction of buprenorphine treatment for opioid dependence. • Maintenance treatment of opioid dependence.	Maintenance treatment: buccal film applied as single daily dose (8.4 mg/1.4 mg)	$3,352
Buprenex *Reckitt Benckiser Pharmaceuticals*	Buprenorphine IM or IV injection	Relief of moderate-to-severe pain.	1 mL (0.3 mg buprenorphine) administered by deep IM or slow (at least two minutes) IV injection at up to six-hour intervals, as needed, in patients 13 years of age and older. Repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage.	$13,107[b]
Butrans *Purdue Pharma*	Buprenorphine transdermal patch	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	• As first opioid analgesic: treatment initiated with 5-mcg/hour patch; worn for seven days. • Conversion from other opioids: initiated with 5- or 10-mcg/hour patch, depending on prior oral morphine equivalent; worn for seven days. • Maximum dosage: 20 mcg/hour.	$1,891[c]
Probuphine *Titan Pharmaceuticals/ Braeburn Pharmaceuticals*	Buprenorphine subdermal implant	Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of transmucosal buprenorphine-containing product.	Four subdermal implants, each containing 74.2 mg of buprenorphine, remain *in situ* for six months and are then removed.	$5,940
Suboxone *Indivior, Inc.*	Buprenorphine/naloxone sublingual film for sublingual or buccal use	Treatment of opioid dependence.	Maintenance treatment: 16 mg/4 mg as single daily dose.	$3,184
Zubsolv *Orexo US, Inc.*	Buprenorphine/naloxone sublingual tablet	Treatment of opioid dependence.	Maintenance treatment: 11.4 mg/2.9 mg as single daily dose.	$3,384

AWP = average wholesale price; IM = intramuscular; IV = intravenous.

[a] AWP of product required in dosing regimen for 180 days, unless otherwise noted.
[b] One 0.3-mg/mL injection every six hours for six months (minimum recommended dosage).
[c] One 5-mcg/hour patch per week for six months (minimum recommended dosage).

several cases of accidental poisonings of small children. Therefore, an implantable product would be less likely to be accidentally ingested by small children, offering another potential advantage of subdermal inplants.[16]

The average wholesale price (AWP) of a six-month course of Probuphine is $5,940.[17] In comparison, the six-month AWP of IV or IM buprenorphine formulations is more than twice that, at an estimated $13,107.[17] Sublingual and transdermal formulations of buprenorphine, on the other hand, are considerably less expensive than Probuphine but do not offer the convenience of twice-yearly dosing along with the other benefits listed above (Table 1).

CONCLUSION

Probuphine implants are the only product currently available for the maintenance treatment of opioid dependence that provides nonfluctuating blood levels of buprenorphine continuously for six months after a single insertion procedure.[7] The clinical benefits of subdermal implants compared with injections, sublingual tablets and films, and transdermal patches include improved compliance, a reduced risk of diversion, less frequent administration, and continuous, nonfluctuating blood levels of buprenorphine.[7]

The labeling for Probuphine includes a boxed warning regarding the potential for implant migration, protrusion, expulsion, and nerve damage associated with insertion and removal. Other potential adverse events include headache, nausea, vomiting, and constipation.[6]

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